SIMPLE PREDICTORS IN IDENTIFYING BACTERIAL PNEUMONIA IN CHILDREN AGED 6 MONTHS TO 60 MONTHS

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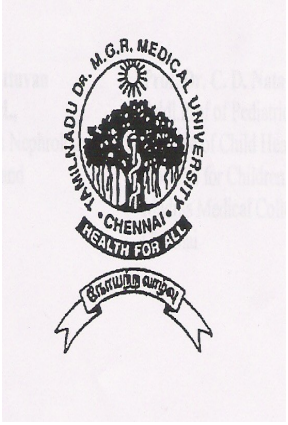

INSTITUTE OF CHILD HEALTH

AND

HOSPITAL FOR CHILDREN
MADRAS MEDICAL COLLEGE
THE TAMIL NADU Dr. M.G.R. MEDICAL UNIVERSITY
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CERTIFICATE

Certified that this dissertation entitled **"SIMPLE PREDICTORS IN IDENTIFYING BACTERIAL PNEUMONIA IN CHILDREN AGED 6 MONTHS TO 60 MONTHS"** is a bonafide work done by **Dr. P. Suresh, M.D**. Postgraduate student of Pediatric Medicine, Institute of Child Health and Hospital for Children, Egmore, Chennai –8 attached to Madras Medical College, during the academic years 2005-2008.

Prof. Dr. Saradha Suresh, M.D., Ph.D., F.R.C.P.(Glas),
Director and Superintendent (I/C),
Head of Department and Professor of Pediatrics,
Institute of Child Health and Hospital for Children,
Madras Medical College,
Chennai.

Prof. Dr. T.P.Kalaniti, M.D.,
Dean,
Madras Medical College,
Chennai.

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CONTENTS

INTRODUCTION

Infections of the respiratory tract are perhaps the most common human ailments. Acute Respiratory Infections (ARI) have quite a high morbidity and mortality in children in developing countries[1]. On an average, children below 5 years of age suffer about 5 episodes of ARIs annually regardless of, where they live, or what their economic situation is, (Kamath and others, 1969, Monto and Ullman 1974) thus accounting for about 228 million attacks, although most of the attacks are mild and self limiting episode. ARI is responsible for about 30-50 percent of visits to health facilities and for about 20-40 percent of hospital admissions. Pneumonia is a leading cause of mortality in children worldwide. Estimates of the mortality burden are problematic.

The World Health Organization (WHO) propose 2-6 million childhood deaths annually attributed to acute lower respiratory tract illnesses (ALRI)[2]. Although the delivery of current and new vaccines is obviously a key issue in the control of ALRI, case management has been the mainstay of international attempts to reduce this burden of disease. During last 20 years, many countries have implemented the case management algorithms developed by the WHO. There is good evidence that such programs have reduced mortality from this condition in developing countries[3]. In the last few years, these and other disease- specific algorithms have been incorporated into the integrated management of childhood illness approach that has been developed by the WHO.

The primary purpose of such an algorithm is to prevent mortality due to bacterial pneumonia. However an unknown proportion of children managed in this fashion will have a viral related wheezing illness or asthma, rather than pneumonia. Although it is

unlikely that wheezing syndromes are a significant cause of mortality for children in developing countries, these algorithms are likely to result in unnecessary administration of antibiotics as well as inadequate treatment of recurrent wheezing illness. If these issues are to be tackled, we need to carefully review the existing evidence about wheezing illness in early life.

There are only a small number of population- based studies on natural history that assess symptoms and lung function in the first six years of life. All these studies are from developed countries. The most important of these is the Tuscan Children Respira - studies commenced in the early 1980s in Arizona, USA[4]. This group prospectively enrolled 1246 newborn children in 1980. Follow-up data was available at both 3 and 6 years of age for 826 children. This study demonstrated that almost 60% of children who were in the first few years of life have ceased wheezing by age 6. Most children with wheeze in the first three years of life have a transient syndrome that may be related to pre-existing reduced airway function at birth and this condition is not associated with features of atopy or future development of asthma.

Non-asthmatic wheeze in early childhood is associated with intercurrent viral illness. The risk factors for this syndrome appear to be:

- Reduced lung function that may reflect impaired lung growth in the intrauterine period.
- Exposure to tobacco smoke either during the prenatal or early childhood period [4,5]

In both developed and developing countries, respiratory Syncytial virus is the predominant etiological agent often responsive for bronchiolitis and wheezing illness in the first 2 years of life [6,7]. Moreover data from several studies demonstrate that RSV infection and the bronchiolitis syndrome are a major component

of the total ALRI in children living in developing countries. The relevant literature on therapy includes studies in which children were labeled as bronchiolitis and others in which children were classified as wheezing illness.

Unfortunately we do not have clear evidence about whether antibiotics can be withheld in some categories of children with tachypnea. It is clear that tachypnea occurs in bacterial infection and in addition, co-infection with virus and bacteria has been well demonstrated in several studies on pneumonia etiology in children. Although some studies have found that children with more severe disease or who are blood culture positive are more likely to be febrile at the time of presentation, these signs are not sufficiently sensitive or specific to determine whether antibiotics should be administered [8,9].

There is substantial evidence that the prevalence of hyper-reactive airway disease is increasing worldwide both in developed and developing countries. A study conducted by a pediatric pulmonologist in metropolitan cities showed steady rise of prevalence from 9% to 29.5% [10,11]. This steady rise in prevalence correlated with demographic changes in this city like increase in industries, increased density of population from migration of rural population in search of jobs and increased number of automobiles to commute resulting in air pollution.

The study concluded that allergic respiratory disorders in particular asthma are increasing in the developing countries and pose a serious global health problem in children and economic burden [11]. WHO developed the programme for the control of respiratory infections in 1980s which was included as a component of the integrated

management of childhood illness strategy in the mid 1990s [12]. This strategy includes utilization of simple clinical signs and symptoms with high sensitivity and specificity to be adopted at first level health facilities by paramedical personnel [12]. Using this algorithm, pneumonia is diagnosed by the presence of tachypnea defined as respiratory rate >60 breaths / minute among children aged <2 months, >50 breaths / minute among children aged 2-11 months and >40 breaths / minute among the children aged 12-59 months.

Because mortality due to pneumonia in developing countries is attributable mainly to bacterial etiology, IMNCI strategy recommends the use of antibiotics when a child presented with tachypnea as defined previously [12]. Despite the proven benefit of this programme, there has been some concern about specificity of the WHO pneumonia algorithm and IMNCI leading to unnecessary use of antibiotics in regions with high prevalence of wheezing illness [14].

In this context, it is also important to consider that asthma and other wheezing illness do occur and they can be diagnosed in children who present with cough and difficult breathing and they can be treated with only bronchodilators without the need for antibiotics [15]. The study was designed to evaluate the potential use of fever, chest indrawing and the effect of bronchodilator response in children with cough and tachypnea as tools to exclude the diagnosis of pneumonia and thus to refine the use of antibiotics.

Acute respiratory infections in children:

Acute respiratory infections (ARIs) are classified as upper respiratory tract infection (URIs) or lower respiratory tract infections (LRIs). The upper respiratory tract consists of the airways from the nostrils to the vocal cords in the Larynx, including the paranasal sinuses and the middle ear. The lower respiratory tract covers the continuation of the airways from the trachea and bronchi to the bronchioles and the alveoli. ARIs are not confined to the respiratory tract and have systemic effects because of possible extension of infection or microbial toxins, inflammation, and reduced lung function.

ARIs are the most common cause of both illness and mortality in children under five, who average three to six episodes of ARIs annually regardless of where they live or what their economic situation is. However the proportion of mild to severe disease varies between high and low income countries resulting in higher case fatality rate. Although medical care can to some extent mitigate both severity and fatality, estimates indicate that in 2000, 1-9 million of them died because of ARIs, 70 percent of them in Africa and South East Asia (Williams and Other 2002). The World health organization with estimates that 2 million children under five die of pneumonia in each year (Bryce and others 2005)[16]

Causes of ARIs and burden of disease:

ARIs in children take a heavy toll in life, especially where medical care is not available or is not sought.

Upper respiratory tract infections:

URIs are the most common infectious disease. They include Rhinitis (Common

cold), sinusitis, ear infections, acute pharyngitis or tonsillo pharyngitis, epiglotitis and laryngitis of which ear infections and pharyngitis cause the more severe complications (deafness and acute rheumatic fever respectively). The vast majority of URIs have a viral etiology. Rhinoviruses account for 25 to 30 percent of URIs respectively syncytial viruses (RSVS), parainfluenza and influenza viruses, human metapneumovirus, and adenoviruses for 25 to 35 percent, corona virus for 10 percent and unidentified viruses for the remainder (Denny, 1995). Because most URIs are self limiting, their complications are more important than the infections. Acute viral infection predisposes children to bacterial infections of the sinuses and middle ear, and aspiration of infected secretions and cells which can result in LRIs (Berman, 1995)[17].

Acute Pharyngitis:

Acute Pharyngitis is caused by viruses in more than 70 percentage of cases in young children. Mild pharyngeal redness and swelling and tonsil enlargement are typical. Streptococcal infection is rare in children under five and more common in older children. In countries with over-crowded living conditions and population that may have a genetic predisposition, post streptococcal sequelae such as rheumatic fever and carditis are common in school age children but may also occur in those under five.

Acute Ear Infections:

Acute ear infection occurs with upto 30 percent of URIs. In developing countries with inadequate medical care, it may lead to perforated eardrums and chronic discharge in later childhood and ultimately to hearing impairment or deafness (Berman 1995b)[17].

Chronic ear infection following repeated episodes of acute ear infection is common in developing countries affecting hearing which may be disabling and may affect learning. Repeated ear infections may lead to mastoiditis, which in turn may spread infection to the meninges. Mastoiditis and other complications of URIs account for nearly 5 percentage of all ARI deaths worldwide (Williams and others 2002)[18].

Lower Respiratory tract infections:

The common LRIs in children are pneumonia and bronchiolitis. Respiratory rate is a valuable clinical sign for diagnosing acute LRI in children who are coughing and breathing rapidly. The presence of lower chest wall indrawing identifies more severe disease (E. Mulholland and Others, 1992; Shann, Heart and Thomas, 1984)[19].

Currently, the most common causes of viral LRIs are RSVs. They tend to be highly seasonal; parainfluenza viruses are the next most common cause of viral LRIs. The epidemiology of influenza viruses in children in developing countries deserves urgent investigations because safe and effective vaccines are available.

Pneumonia:

Both bacteria and viruses can cause pneumonia. Bacterial pneumonia is often caused by streptococcus pneumoniae (pneumococcus) or haemophilus influenza mostly type b (Hib) and occasionally by staphylococcus aureus or other streptococcus. Just 8 to 12 of the many types of pneumococcous cause most cases of bacterial pneumonia although specific types may vary between adults and children and between geographic locations. Other pathogens such as mycoplasma pneumonia and chlamydia pneumonia

cause atypical pneumonias.

Upper respiratory tract colonization with potentially pathogenic organisms and aspiration of the contaminated secretions have been implicated in the pathogenesis of bacterial pneumonia in young children. Infection of the upper respiratory tract with influenza virus or RSVs has been shown to increase the binding of both H. influenza (Jiang and others, 1999)[20] and streptococcus pneumoniae (Hament and others 2004; McCuller and Bartmess)[21] to lining cells in the nasopharynx.

This finding may explain the increased rates of pneumococcal pneumonia parallel to influenza and RSV epidemics. Viruses are responsible for 40 to 50 percent of infection in infants and children hospitalized for pneumonia in developing countries. Measles virus, RSV, parainfluenza viruses, influenza type A virus and adenoviruses are the most important cause of viral pneumonia. Differentiating between viral and bacterial pneumonias radiologically is difficult, partly because the lesions look similar and partly because bacterial super-infection occurs with influenza, measles, and RSV infections (Ghafoer and Others, 1990)[22].

Bronchiolitis:

Bronchiolitis occurs predominantly in the first year of life with decreasing frequency in the second and third years. The clinical features are rapid breathing and lower chest wall indrawing, fever in one-third of cases and wheezing (cherian and Other, 1991)[23]. Inflammatory obstruction of the small airways, which leads to hyperinflation of the lungs and collapse of segments of the lung occur. Because the signs and symptoms

are also characteristic of pneumonia, health workers may find differentiating between bronchiolitis and pneumonia difficult. Two features may help are a definition of seasonality of RSV in the locality and the skill to detect wheezing. RSV is the main cause of bronchiolitis worldwide and can cause upto 70 to 80 percent of LRIs during high season (Simoes, 1999, Stentralle, Devasundram and Simoes 2003)[24]. The recently discovered human metapneumovirus also causes bronchiolitis that is indistinguishable from RSV disease. Other viruses that cause bronchiolitis include para-influenza virus type 3 and influenza viruses.

Interventions:

Interventions to control ARIs can be divided into four basic categories:

- Immunization against specific pathogens.
- Early diagnosis and treatment of disease.
- Improvement in nutrition.
- Safer environments.

Vaccinations:

Widespread use of vaccines against measles, diphtheria, pertussis, Hib, pneumococcus, and influenza have the potential to substantially reduce the incidence of ARIs in children in developing countries.

The efficacy of Hib vaccine in preventing invasive disease has been well

documented in several studies in industrialized countries.

In developing countries, the vaccine is likely to have greater effect in preventing LRIs, including bacteraemic pneumonia.

Case management:

The simplification and systematization of case management for early diagnosis and treatment of ARI have enabled significant reductions in mortality in developing countries where access to pediatricians is limited. WHO guidelines for ARI care management (WHO, 1991) use two key clinical signs- respiratory rate to distinguish children with pneumonia from those without, and lower chest wall indrawing to identify severe pneumonia requiring referral and hospital admission. Children without these signs are classified as having ARI but not pneumonia. Children showing only rapid breathing are treated for pneumonia. Children with pneumonia are treated with out-patient antibiotic therapy. Children who have cough for more than 30 days are referred for further assessment of tuberculosis and other chronic infection.

Pneumonia Diagnosis based on rapid breathing:

The initial guidelines for detecting pneumonia based on rapid breathing were developed in Papua New Guinea during the 1970s. WHO recommends a respiratory rate cut-off of 50 breaths per minute for infants aged 2 through 11 months and 40 breaths per minute for children age 12 months to 5 years.

Rapid breathing as defined by WHO, defects about 85 percent of children with

pneumonia, and more than 80 percent of children with potentially fatal pneumonia are probably successfully identified and treated using the WHO diagnostic criteria. Antibiotic treatment of children with rapid breathing has been shown to reduce mortality. The problem of the low specificity of the rapid breathing criterion is that some 70 to 80 percent of children who may not need antibiotics will receive them.

Pneumonia diagnosis based on Chest wall indrawing:

Children are admitted to hospital with severe pneumonia when health workers believe that oxygen or parenteral antibiotics are needed or when they lack confidence in the mother's ability to cope. The rationale of parenteral antibiotics is to achieve a higher level of antibiotics and to overcome concerns about the absorption of oral drugs in ill children.

The papua new guinea study (Shann, Harl and Thomas 1984)[25] used chest wall indrawing as the main indicator of severity, but studies from different parts of the world show larger differences in the rates of indrawing because of variable definitions. Restriction of the term to lower chest wall indrawing, defined as inward movement of the bony structures of chest wall with inspiration has provided a better indicator of the severity of pneumonia and one that can be taught to health workers. It is more specific than intercostal indrawing which frequently occurs in bronchiolitis.

Studies in the Philippines and Swaziland (E. Mulholand and other, 1992)[19] found that lower chest wall indrawing was more specific than intercostal indrawing for a diagnosis of severe pneumonia requiring hospital admission. In the Vellore study

(Cherian and Other, 1988)[26] lower chest wall indrawing correctly predicts 79 percent of children with LRI who were hospitalised by a pediatrician.

Antimicrobial options for oral treatment of pneumonia:

The choice of an antimicrobial drug for treatment is based on the well established findings that most childhood bacterial pneumonia are caused by S. pneumoniae or H. influenza. WHO has technical documents to help assess the relevant factors in selecting first and second line antimicrobials and comparisons of different microbials in relation to their antibacterial activity, treatment efficacy and toxicity.

The emergence of antimicrobial resistance in S.pneumoniae and H. influenzae is a serious concern. In some settings, in-vitro tests show more than 50 percent of respiratory isolates of both bacteria resistant to co-trimoxazole, and penicillin resistance to S. pneumoniae is gradually becoming a problem worldwide. Amoxycillin is concentrated in tissues and in macrophages and drug levels are directly correlated with oral dosages. Therefore higher doses than in the past given twice a day are now being used to successfully treat ear infections caused by penicillin resistant S.pneumoniae and in the face of higher rates of cotrimoxazole resistance, amoxycillin may be superior for children with severe pneumonia.

Treatment Guidelines:

Current recommendations are cotrimoxazole twice a day for 5 days for pneumonia and intramuscular penicillin or chloramphenicol for children with severe pneumonia. The problems of increasing resistance to cotrimoxazole and unnecessary referral of

children with any chest wall indrawing have led to studies exploring alternative to the antibiotics currently used in ARI care management. With respect to the duration of antibiotic treatment, studies in Bangladesh, India and Indonesia indicate three days of oral co-trimoxazole or amoxycillin are as effective as five days of either drug in children with non-severe pneumonia (Agarwal and Others; Kartasamita 2003)[27].

In a Multicentric study of intramuscular penicillin versus oral amoxicillin in children with severe pneumonia and, where supply is limited, to children with any of the following signs; inability to feed and drink, cyanosis, respiratory rate greater than or equal to 70 breaths per minute, or severe chest wall retractions. Oxygen should be administered at a rate of 0.5 litre per minute for children younger than 2 months and 1 litre per minute for older children. INHO recommends simple clinical signs to detect and treat hypoxemia. Despite there recommendations, a study of 21 first level facilities and district hospitals in seven developing countries found more than 50 percent of hospitalized children with LRI were inappropriately treated with antibiotics or oxygen (Nolan and Others, 2001) and in several, oxygen was in short supply[28].

LITERATURE REVIEW

i) Simple predictors to differentiate acute asthma from ARI children

Sachdev HP et al conducted a study to evaluate simple predictors to differentiate these two conditions to refine the recommended case management. In a case-control comparison, children between 6 months to 50 months age who presented with cough and rapid breathing due to asthma (n=100), ARI (n=100) were evaluated. Only 34% of asthmatics had an audible wheeze. Significant independent predictors on multiple logistic regression analysis were, number of earlier attacks and fever (or temperature). The best predictor for asthma was two or more earlier similar episodes (sensitivity 84%, specificity 84%) followed by temperature <37.6 degree C (Sensitivity 73%, specificity 84%). It is concluded that simple clinical predictors can differentiate acute asthma and ARI.

ii) Respiratory rate and signs in roentgenographically confirmed pneumonia among children in China.

Dai Y et al studied clinical signs in the diagnosis of radiologically confirmed pneumonia among 54 children under 5 years of age. The mean respiratory rate among children with cough and fever was 50 breaths/min for infants, 40 breaths/min for children aged 1-5, compared with 40/min and 30/min respectively for no pneumonia children. The researchers deemed these rates to be the cutoff criterion for rapid breathing. Nasal flaring, chest indrawing and cyanosis had high specificities.

(iii) Improving antibiotic and bronchodilator prescription in children presenting

with difficult breathing- experience from an urban referral hospital.

Sachdev Hp et al conducted a prospective observational study in urban tertiary care centre. Two hundred children aged between 6 months and 5 years presenting with difficult breathing (as defined by WHO algorithm) were prospectively evaluated for the diagnosis and the need for bronchodilator and antibiotic therapy.

On the basis of reliable predictors (sensitivity > 70% and specificity > 70%) of antibiotic and bronchodilator prescription, irrespective of the exact diagnostic category, two viable modifications of WHO case management algorithm emerged - (i) previous similar episode of cough and difficult breathing, and (ii) fever. Acute asthma was the predominant condition (46% or 54%), pneumonia alone was rare (10%), co-existence of pneumonia with bronchospasm was more frequent (22% or 15%). The study concluded that it is feasible to amalgamate these simple clinical features in the WHO case management algorithm to significantly refine the antibiotic (95% CI range 7% to 33%) and bronchodilator (35%; 95% CI 27% to 43%) prescription.

iv) Additional markers to refine the word health organization algorithm for diagnosis of pneumonia:

Castrol AV et al conducted a prospective study in urban tertiary care hospital to examine the value of history of previous respiratory distress, chest indrawing and fever and response to bronchodilator to refine these guidelines. Children aged between 6 months and 59 months presenting with cough and tachypnea (182 children) were enrolled. Each child had a chest x-ray done that was read by two blinded, independent radiologists. Discordance between two radiologists led to excluding 17 patients. The

remaining 165 children were examined for fever and/or chest indrawing and if they had a history of previous respiratory distress, challenged with bronchodilator.

The association of persistent tachypnea after bronchodilator and presence of pulmonary infiltrate was recorded. Pneumonia was radiologically diagnosed in 26/165 (15.8 percent). 2/40 (5%) of children without history of previous respiratory distress had pneumonia. Of the 125 children with history of previous respiratory distress, pneumonia was identified in 24 (19.2%). Persistence of tachypnea after bronchodilator was associated with pulmonary infiltrate in 14/24 (58.3 percent) whereas tachypnea persisted in 32/101 (37%) children without pulmonary infiltrates ($p = 0.02$). The negative predictive value of resolution of tachypnea was 87%. Bronchodilator non-response was most useful in children without fever and or with chest indrawing to indicate pneumonia as the cause of tachypnea.

This study indicates that by adding the simple procedures of a history of previous respiratory distress, recording of fever and chest indrawing, and observing the response to bronchodilators, pneumonia can be reliably identified in children presenting with tachypnea and cough. It is probable that this approach to management of children with cough and tachypnea could reduce unnecessary use of antibiotics.

v) White blood cell count can aid judicious antibiotic prescribing in acute respiratory infection

Casey et al did a prospective study in New York USA. The use of the WBC count was assessed, including obviating antibiotic prescription, frequency of related follow-up visits, and the occurrence of subsequent bacterial infections.. Of the 1956 children with respiratory or febrile illness enrolled, 1219 (62%) had diagnosis established by history

and examination and 737 (38%) did not. Of the 737 patients without an established diagnosis, 386 (52%) did not receive an antibiotic because they did not appear particularly ill, their temperature was less than 101 degrees F, and parents were not demanding antibiotics, leaving 351 (48%) patients who appeared ill, had a temperature greater than 101 degrees F, and parents were demanding an antibiotic or physicians were inclined to give an antibiotic.

A WBC count was performed on these 351 children; 337 children (96%) had a WBC count less than 15,000/mm3, and 14 (4%) had a WBC 15,000/mm3 or greater. An antibiotic was prescribed for 13 of the 14 children with a WBC count greater than 15,000/mms. With this approach, return office visits in the following 2 weeks were infrequent (13% of 737 patients), and no child had significant bacterial illness that was missed with selective use of WBC count testing.

vi) Role of X-ray in diagnosis of lower respiratory infection in children:

Shaikh et al study in Pakistan in children with cough and fever in established clinics were investigated with oro-pharyngeal swabs, blood culture, and chest radiograph. 6383 children were studied. Of these, 1203 children had pneumonia and severe pneumonia. Chest radiograph was taken in 823 children only. 45% of these radiographs had signs suggestive of infection. There was no correlation between reports of radiograph and isolation of organisms from oro-pharyngeal swabs. Nearly half of the children with pneumonia and those who grew organisms from oro-pharyngeal swabs had normal chest radiographs. The study concluded that chest radiographs have little value in diagnosis of pneumonia in children less than the year of age in community level.

vii) Assessment and management of children aged 1-59 months presenting with wheeze, fast breathing and/or lower chest indrawing - results of a multicentric descriptive study in Pakistan

Hazir T et al did a multicentric prospective study in children aged 1-59 months with auscultatory and audible wheeze and fast breathing and lower chest wall indrawing. Response to three cycles of inhaled bronchodilators and followed up on day 3 and 5. A total of 1622 children with wheeze were screened from may 2001 to April 2002, of which 1004 (61.8%) had WHO defined non severe pneumonia, 618 (32.8%) had severe pneumonia. 621 (61.8%) responded to upto three cycles of bronchodilators.

Of the 618 severe pneumonia, only 166 (26.8%) responded. Among responders, 93 (14.9%) in the non-severe pneumonia and 63(37.9%) children in the severe pneumonia group showed subsequent deterioration on follow-up. No family history of wheeze, temperature >100ºF and lower chest wall indrawing were identified predictors of subsequent deterioration. This study concluded that two thirds of children with wheeze are not identified by current WHO ARI guidelines. Antibiotics are over-prescribed and bronchodilators are under-utilized in children with wheeze.

STUDY JUSTIFICATION

Most of the fevers with respiratory illness are virus associated and self limiting. Routine blood investigation and radiological imaging are not required and increases the cost of the treatment.

This study is expected to describe the distribution of disease in fever with respiratory distress in tertiary care hospital, to find additional markers to identify and predict pneumonia in children with tachypnoea.

AIM OF THE STUDY

- To re-define or refine tachypnea as a specific indicator of bacterial pneumonia.
- To identify other clinical predictors for identifying bacterial pneumonia.

SUBJECTS AND METHODS

The study was designed to be done in two phases. In the first phase it is to be carried out as a descriptive study of children presenting with fever and respiratory distress in the OPD to identify the specific markers for bacterial pneumonia. In the second phase presenting clinical features in children with radiological pneumonia will be analysed to validate the findings from Phase I.

Study period **:** Nov. 2006 to Oct. 2007

Study place **:** Institute of Child Health and Hospital for Children, a tertiary care hospital in Chennai

Phase I
Sample size **:** 100 children

Study population: *Children presenting in the out patients department with fever and respiratory distress.*

Inclusion Criteria:

Children in the age group 6 months to 5 years with pneumonia as defined by the WHO i.e. children with the following symptoms

- Fever <5 days and
- Cough & cold < 1 week
- Age specific tachypnea with or without lung signs (wheeze or crepts) i.e.
    - ≥50 breaths/min in 2 months to 11 months
    - ≥40 breaths/min in 12-60 months
- Indrawing of chest

Exclusion Criteria:

- Child with severe illness as defined by WHO like not able to take oral feed, stridor in a calm child, severe malnutrition, convulsions, abnormal sleepy
- Children with an established diagnosis of bronchial asthma
- Children who had similar illness in the last 2 weeks
- Antibiotics used in the last 2 weeks.
- Children with established diagnosis of other chronic illness like congenital heart disease, tuberculosis.
- Immunodeficient children, or on steroid therapy.
- Children with respiratory failure
- Children who were intubated and ventilated
- Children requiring inotropic support

Manoeuvre:

Children in the age group of 6 months to 5 years satisfying the above criteria were enrolled in this phase of the study. A lower age limit of 6 months was used because the diagnosis of hyper-reactive airway disease below this age is uncommon and the likelihood of pneumonia is more in younger infants. Children attending the out-patient department on a fixed day of the week (Monday) and who come under the study population during the study period were admitted and recruited in the study and

informed verbal consent for participation was taken from the parents.

Clinical and Investigative Evaluation:

The detailed clinical evaluation of these subjects, done by a single observer was recorded on the proforma. Special emphasis was given to symptoms like cough, fever, nasal discharge, tachypnea, chest indrawing, and refusal of feeds.

On physical examination:

The following were specifically looked for

- Toxic look (investigator's impression)
- Temperature: Axillary temperature (in degree Celsius) was recorded for 3 minutes.
- Pulse rate: Counted by palpating radial pulse for 60 seconds.
- Respiratory rate: Counted by observing the movement of chest and abdomen for 60 seconds in an awake but quite child.
- Chest indrawing by observing the inward movement of the bony structure of the lower chest wall during inspiration.
- Nasal discharge if present was classified into watery, mucopurulent or purulent.

Examine chest to look especially for breath sounds and added sounds like crepitations and wheeze. For wheeze, it was also ascertained prior to auscultation, whether the sound was audible without the stethoscope.

i) Abdomen- Liver and spleen were noted.

ii) Other systemic examination was also conducted.

Investigations performed in all subjects include chest roentgenogram and total count and peripheral smear.

Treatment:

All cases admitted were given supportive treatment, which include

- oxygen, if not maintaining saturation
- antipyretics, if febrile
- intravenous fluids, if not able to take orally,
- bronchodilators (aerosolized beta-2-agonist), or steroids if wheeze is present.
- Normal saline nasal drops if nasal symptoms are present

The cases were monitored for any worsening or improvement every 6^{th} hourly on day 1 and vital parameters were monitored. When the clinical condition is not improving or x-ray chest suggests pneumonia, antibiotics were started.

Radiological Evaluation:

Evaluation of the chest was done by a radiologist who was unaware of the clinical diagnosis.

Phase - II

Sample size:

50 children

Study population:

Inclusion criteria:

Children of both sexes in the age group 6 months to 60 months with radiologically diagnosed pneumonitis and pneumonia

Exclusion criteria:

- Child with severe illness as defined by WHO like not able to take oral feed, stridor in a calm child, severe malnutrition, convulsions, abnormal sleepy
- Children with an established diagnosis of bronchial asthma
- Children who had similar illness in the last 2 weeks
- Antibiotics used in the last 2 weeks.
- Children with established diagnosis of other chronic illness like congenital heart disease, tuberculosis.
- Immunodeficient children, or on steroid therapy.
- Children with respiratory failure
- Children who were intubated and ventilated
- Children requiring inotropic support

Manoeuvre:

Children attending the out-patient department on a fixed day of the week (Monday) and who come under this study population during the study period were admitted and recruited in the study and informed verbal consent for participation was taken from the parents. Their clinical profiles were recorded as in phase I. All children coming under this study population were given antibiotics and supportive treatment. The

cases were monitored for any worsening or improvement every 6th hourly on day 1 and vital parameters were monitored.

Diagnostic Definitions:

No universally acceptable criteria are available to objectively define pneumonia[35]. Pneumonia is known to occur without cough, respiratory distress or obvious radiological abnormalities. Conversely, infiltrative changes in the x-ray are possible even in bronchiolitis or asthma[35]. Since the WHO guidelines are intended to rationalize case management in a simplified manner for paramedical personnel, the diagnostic capabilities of trained pediatricians with access to investigations could reasonably be considered as the 'gold standard' for this purpose. In this context, the following operational definitions of pneumonia, asthma and bronchiolitis were resorted.

Pneumonia:

- Fever of more than 100°F with cough alongwith respiratory distress, crepts, and/or wheeze and
- Chest X-ray evidence of pneumonia.

Asthma:

First attack of wheeze after 1 year of age fulfilling following criteria:

- wheeze
- Absence of pulmonary infiltrates on chest x-ray

- Absence of polymorphonuclear leucocytosis or bandemia on peripheral smear.
- Rapid clinical improvement on bronchodilator therapy without antibiotics.

Bronchiolitis:

According to the WHO guidelines, the first attack of wheeze in early infancy is regarded as bronchiolitis. This definition of bronchiolitis was utilized if the peripheral smear failed to reveal a polymorphonuclear response or bandemia or an X ray evidence of bow sign was present.

STATISTICAL ANALYSIS

Results were tabulated and percentage proportion for epidemiological and clinical symptomatolgy were arrived.

For both groups comparative student's 't' test was used to compare the data between the pneumonia group and no pneumonia group. p-value <0.05 was considered significant.

Receiver- operator characteristic (ROC) curve done for temperature, respiratory rate and leucocyte count was done to define cut-off point to predict pneumonia using SPSS software.

RESULTS

Phase – I

Children recruited with WHO defined pneumonia - 100.

Children with WHO defined pneumonia having x-ray evidence of pneumonia – 5

Phase – II

Children identified to have x-ray evidence of pneumonia 50.

Epidemiological Data:

PHASE I

Age Distribution

Age in Months	No of Children	Percentage
6-11	39	39%
12-60	61	61%

PHASE II

Age in Months	No of Children	Percentage

6-11 M	23	46%
12-60	27	54%

In WHO defined pneumonia group, 39 children (39%) were between 6 months to 11 months, and 61 children (61%) were between 12-60 months.

In radiologically defined pneumonia group, 23 children (46%) were in the age group 6-11 months and 27 children (54%) were in the age group 12 months to 60 months.

Sex Distribution:

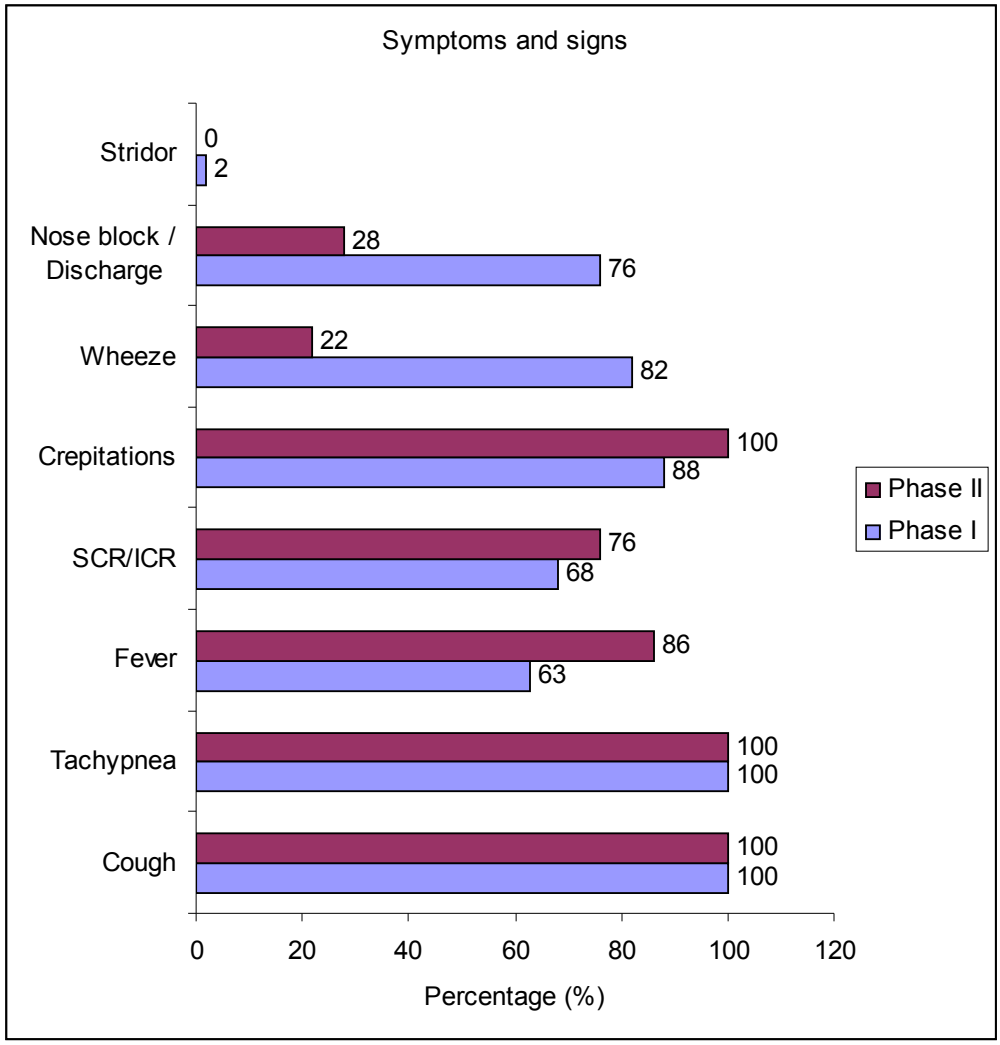
Phase	**Male**		**Female**	
	No.	**%**	**No.**	**%**
Phase I	56	56	44	44
Phase II	26	52	24	48

There was equal distribution of the study population between both the sexes. No sexual preference was noted in ARIs. In child with WHO defined pneumonia, there were 56 males (56%) and 44 females (44%). In radiologically defined pneumonia group, there were 26 male children (52%) and 24 female children (48%).

The male female ratio was 56:44 (1.27:1) in the phase I study, and 52:48 (1.08:1) in the phase II study. This difference is not statistically significant.

Clinical Examination:

Symptoms and signs	**Phase I n=100**		**Phase II n=50**	
	No.	**Percentage**	**No**	**Percentage**
Cough	100	100%	50	100%
Tachypnea (age specific)	100	100%	50	100%
Fever	63	63%	43	86%
SCR/ICR	68	68%	38	76%
Crepitations	88	88%	50	100%
Wheeze	82	82%	11	22%
Nose block / Discharge	76	76%	14	28%
Stridor	2	2%	0	0%



In Phase I study group, tachypnea and cough were present in all children. Fever was present in 63% and subcostal and intercostal retractions were identified in 68%. Wheeze and crepitations are seen in 82% and 88% respectively. Majority of the children had nasal block or nasal discharge (76%). The above-said symptoms were significantly higher in the phase I study than the phase II study.

In phase II study, cough, tachypnea and crepitations were seen in all children. Fever was the predominant symptom in 86% and retractions in 76% of the study population.

In WHO defined pneumonia group, leucocytosis was present in 22 children.(22%)

In radiologically defined pneumonia group, 36 children (72%) have leukocytosis.

Total Count	Normal		Abnormal	
	n	%	n	%
Phase I	78	78%	22	22%
Phase II	14	28%	36	72%

X-ray Findings in Phase I: n %

Bronchiolitis	34	34%
BHI	61	61%
Bronchopneumonia	5	5%

Comparisons of children with no pneumonia and pneumonia

In view of the fact that majority of the x rays were normal and we have a group where there is a x ray evidence of pneumonia, an attempt was made to define those who are likely to have bacterial pneumonia with the three parameters namely, respiratory rate, fever and leukocytosis.

Comparison of parameters in the 6-11 months age group

Parameter	Mean ± SD		p-value
	No pneumonia	Pneumonia	
RR	55 ± 2	56 ± 2	0.00
Temperature	37.1± 0.7	38.2 ± 0.5	0.00
WBC	14418 ± 2568	17708 ± 1750	0.00

Mean respiratory rate for 6-11 months were 55 ± 2 in no pneumonia group and 56 ± 2 in pneumonia group. Mean temperature for 6-11 months were 37 ± 0.7 in no pneumonia group and 38.2 ± 0.5 in pneumonia group. Mean leukocyte count for 6-11 months were 14418 ± 2568 in no pneumonia group and 17708 ± 1750 in pneumonia group.

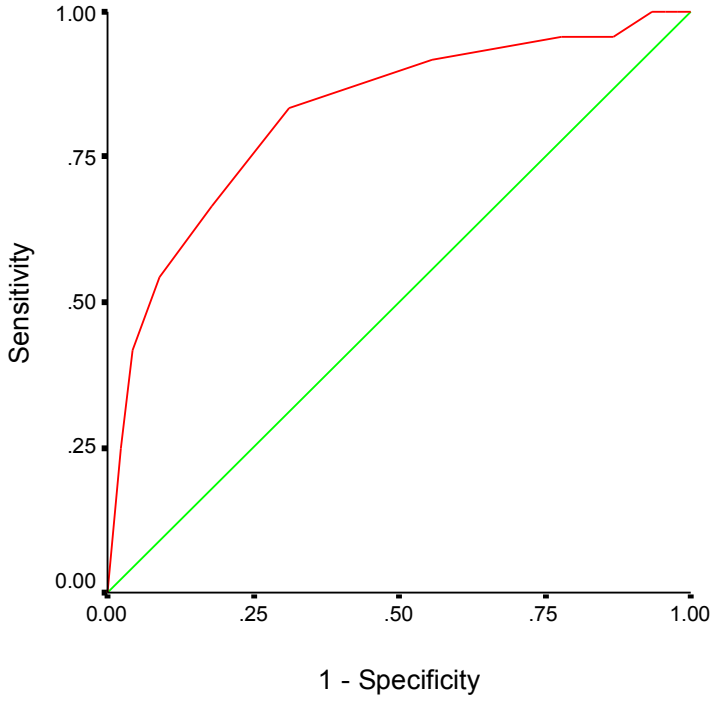
Comparison of parameters in the 12-60 months age group

.Parameter	Mean ± SD		p-value
	No pneumonia	Pneumonia	
RR	44 ± 2	46 ± 2	0.04
Temperature	37.2± 0.8	38.2 ± 0.4	0.00
WBC	12016 ± 2638	15304 ± 2148	0.00

Mean respiratory rate for 12-60 months were 44 ± 2 in no pneumonia group and 46 ± 2 in pneumonia group. Mean temperature for 12-60 months were 37.2 ± 0.8 in no pneumonia group and 38.2 ± 0.4 in pneumonia group. Mean leukocyte count for 12-60 months were 12016 ± 2638 in no pneumonia group and 15304 ± 2148 in pneumonia group.

Development of ROC for predicting RR cutoff value for 6 – 11 months.

The ROC was developed to predict the cut-off values for respiratory rate, temperature and leukocytosis.

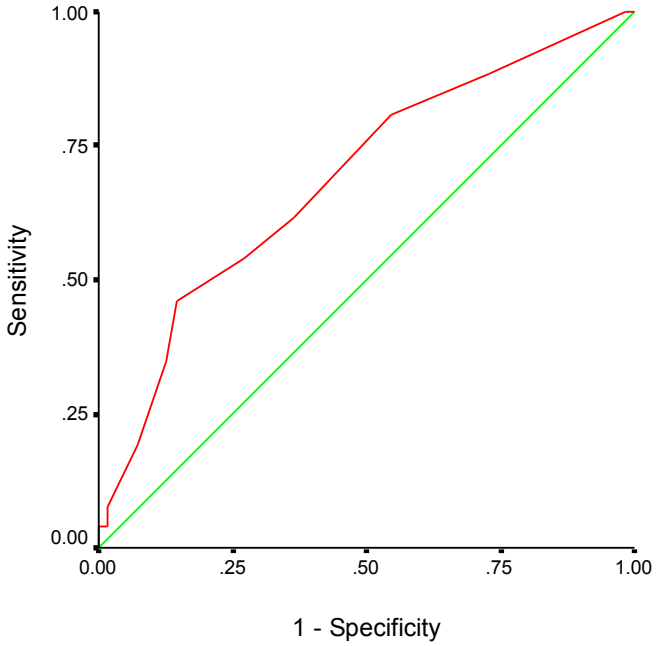


Area under the curve = 0.83 (95% C.I. = 0.72, 0.93) (p-value = 0.00)

The best cut off lies at 53.5 with a sensitivity of 83% and specificity o 68.9%

An area of 0.83, for example, means that a randomly selected child with pneumonia has a RR larger than that for a randomly chosen child without pneumonia 83% of the time.

Development of ROC for predicting RR cutoff value for 12 months – 60 months

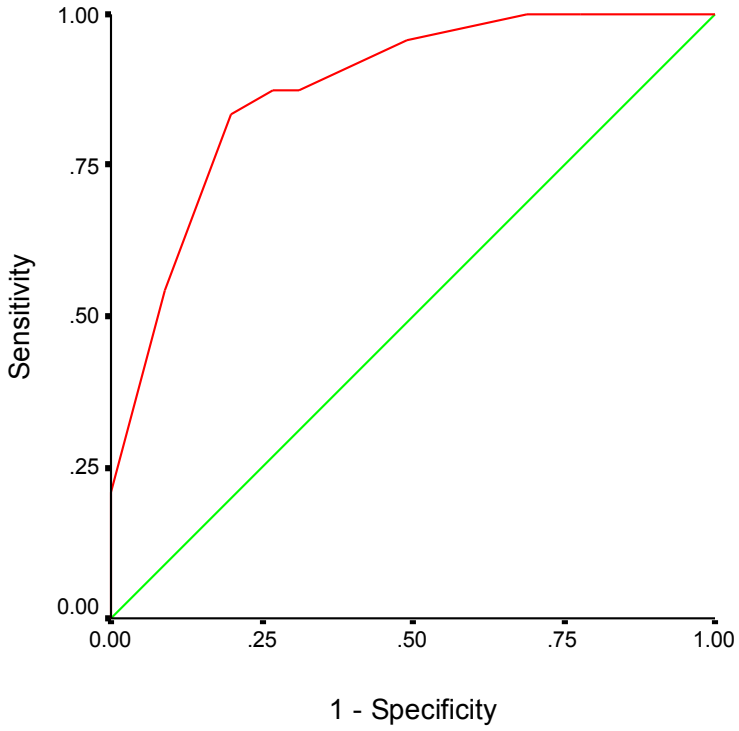


Area under the curve = 0.69 (95% C.I. = 0.56 , 0.81) (p-value=0.01)

The best cut off lies at 43.5 with a sensitivity of 80.8% and specificity of 45.5%

An area of 0.69, for example, means that a randomly selected child with pneumonia has RR larger than that for a randomly chosen child without pneumonia 69% of the time.

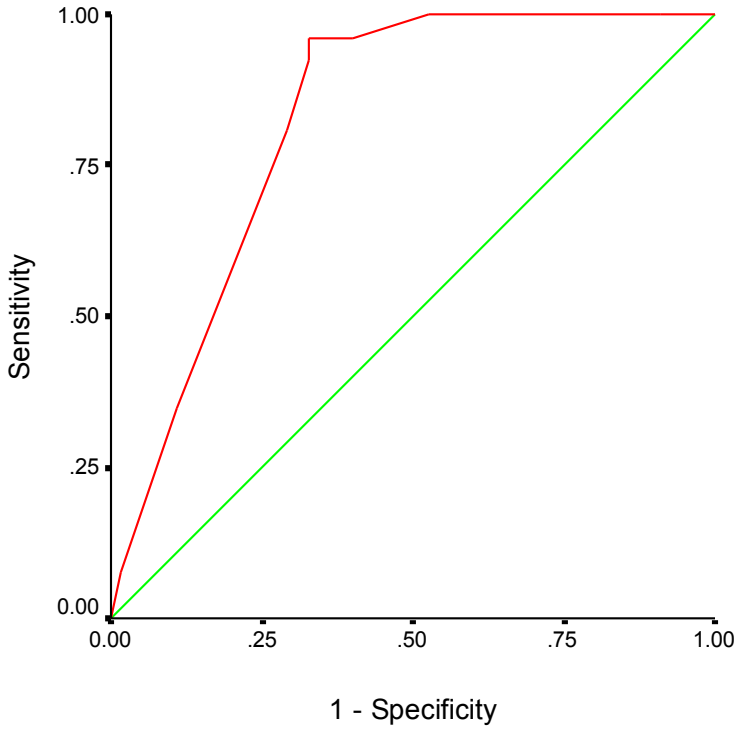
Development of ROC curve for temperature between 6 months -11 months.



Area under the curve = 0.88 (95% C.I. = 0.79, 0.96) (p-value=0.00)

The best cut off lies at 37.6^{o} C with a sensitivity of 88% and specificity of 73.3%

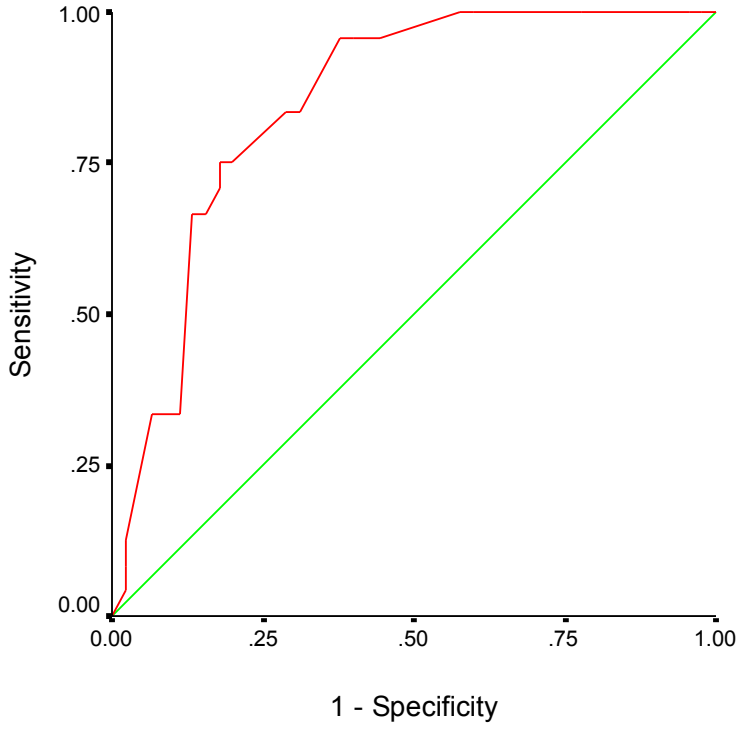
Development of ROC curve for temperature between 12 months -60 months.



Area under the curve = 0.82 (95% C.I. = 0.74, 0.91) (p-value=0.00)

The best cut off lies at 37.6 with a sensitivity of 92% and specificity of 67.3%

Development of ROC curve Leucocytosis for 6 months – 11 Months



Area under the curve = 0.85 (95% C.I. = 0.76, 0.94) (p-value=0.00)

The best cut off lies at 16250 with a sensitivity of 75% and specificity of 80%

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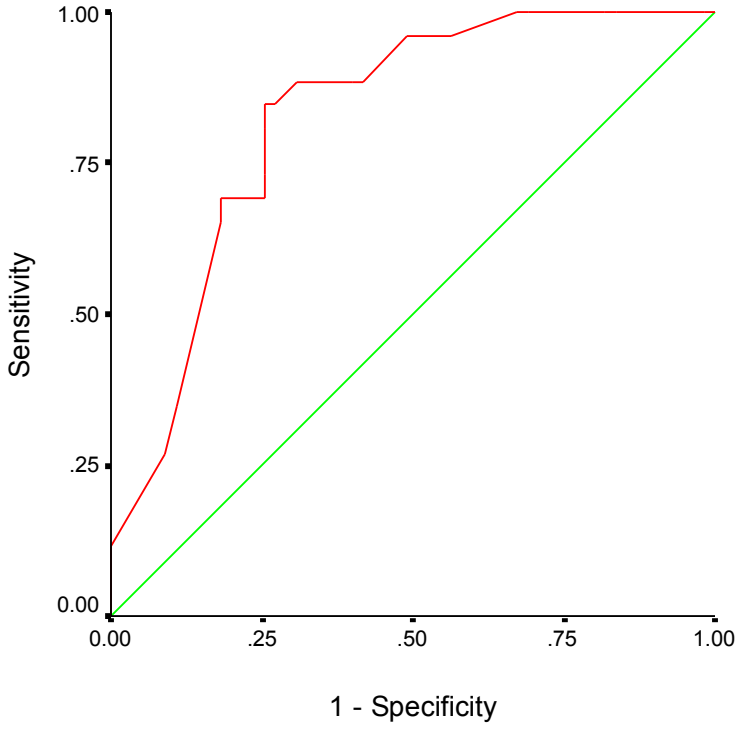
Development of ROC curve Leucocytosis for 12 months – 60 Months



Area under the curve = 0.82 (95% C.I. = 0.74, 0.91) (p-value=0.00)

The best cut off lies at 13650 with a sensitivity of 73% and specificity of 74.5%

Accuracy is measured by the area under the ROC curve. An area of 1 represents a perfect test; an area of .5 represents a worthless test. A rough guide for classifying the accuracy of a diagnostic test is the traditional academic point system:

- .90-1 = excellent (A)
- .80-.90 = good (B)
- .70-.80 = fair (C)
- .60-.70 = poor (D)
- .50-.60 = fail (F)

Outcome:

Children with no pneumonia treated only with supportive care showed symptomatic improvement in wheeze and respiratory distress in 10-14 hrs with quick response to bronchodilators and in bronchiolitis within 24-48 hrs and in bronchopneumonia within 2-4 days. No deaths were observed in both the study groups.

DISCUSSION

Pneumonia has been a major cause of mortality in under five age group, accounting for 14.3% deaths in infancy and 15.9% during 1-5 years. Pneumonia was mainly diagnosed by clinicians based on clinical findings and x-ray evidence. Majority of the children in developing countries do not have access to either a skilled person or to radiological investigations. By the time they reach either of these, it is too late for the child with many fold increase in risk of mortality.

It was such a scenario that various clinical parameters were assessed by various group of researchers, age specific tachypnea was identified as the single most sensitive indicator of pneumonia. Various community based study proved (The Papua New Guinea study, (Shann, Hard and Thomas, 1984)[26] and Cherian and others, 1988 in India and (Mulholland and others, 1992)[19]. On the basis of these and other data (Cambell, Byass and others 1989), Kolstad and others, 1997, Perkins and others, 1997[16] , Redd 1994, Simoes and other 1997,[24] Weber and others, 1997). WHO recommends respiratory rate cut-off 50 breaths per minutes for infants age group 11 months and 40 breaths per minute age 12 months to 60 months).

The skill of simple counting of respiratory rate can be easily acquired by health care provider at primary health centre level. WHO developed algorithm for ARI management based on tachypnea, chest indrawing and danger signs. This WHO based protocol has been very effective in reducing mortality due to pneumonia. However tachypnea was not a specific indicator and could be due to other conditions like viral

pneumonias and bronchiolitis and allergic airway disease etc.

In India, especially in southern states, the last decade has witnessed rapid phase of industrialization, change in life style and upward mobility of the populations. Industrial houses have been setting up factories in rural areas thereby increasing the changes of pollution and hyper-reactive airway disease. In such a scenario, it is but natural for more cases of hyper-reactive airway disease and viral pneumonia to occur.

It is against this background that WHO defined pneumonia was revisited by this study to refine the parameters in order to filter out allergic airway disease and viral pneumonia. Over-use of antibiotics and non-usage of supportive measures like nebulization could result in higher cost and morbidity and mortality.

Pneumonia and other airway disease affect the infants much more than older children. This has been proved in study conducted by V.P.Reddaiah and S.K.Kapoor[38] in AIIMS in India. 47.7% of pneumonia occur in infants. 87.7% occurred in children below 3 years. Males had a relatively higher incidence of pneumonia (0.32 Vs 0.27).

And it has been confirmed by this study. In our study, the infants constituted 46% of the total pneumonias and the 12 to 60 month age group constituted 54%. There is no sex prediction for the affliction with airway illness. Clinical triad of fever, breathlessness, and cough is common to both the groups as proved by our study. However among the No pneumonia group, fever, wheeze, and nasal discharge seem to be the commonest presentation. N.Shimojo et al[39] study found that the association of wheezing illness with allergic rhinitis is about 35 to 48%.

Three clinical parameters respiratory rate, fever and one lab parameter, leukocytosis are found to be significantly different between pneumonia and no pneumonia group especially after nebulisation. Thus if tachypnea, which is a simple clinical parameter which can be easily practised in primary care settings can be redefined and temperature, again a simple clinical parameter which can be easily practised to identify bacterial pneumonias, it could cause a significant reduction in cost of management and over-use of antibiotics and better utilization of supportive therapy.

Receiver-operator characteristic curve was developed for the parameters of tachypnea, fever and leukocytosis.

For the children 6-11 months, respiratory rate of 53.5 and above was found to predict pneumonia with a sensitivity of 83% and specificity 68.9% (95% C.I = 0.72, 0.93) (p-value:0.00).

For children 12-60 months cut-off rate of 43.5 with a sensitivity of 80.8% and specificity of 45.5% (95% C.I. = 0.56, 0.81) (p-value:0.01).

For children 6-11 months, temperature 37.6ºc and above was found to best predictor of pneumonia with sensitivity of 88% and specificity of 73.3% (95% C.I. = 0.79, 0.90) (p-value: 0.00).

For children 12-60 months, the best cut-off value of temperature at 36.6ºc and above with sensitivity of 92% and specificity of 67.3% (95% C.I.=0.74, 0.91) (p-value:0.00).

For children 6-11 months, leukocytosis of 16250 and above was found to predict pneumonia with sensitivity of 75% and specificity of 80% (95% C.I.= 0.76, 0.94) (p-value: 0.00).

For the children 12 months to 60 months, leukocytosis of 13650 and above with sensitivity of 73% and specificity of 74.5% (95% CI=0.74, 0.91) (p-value = 0.00).

The similar study done by Naresh Kumar et al [40] in a tertiary care hospital found that 88% infants having bronchopneumonia had fever >100ºF and only 12% infants had temperature <100ºF. Presence of fever >100ºF had a sensitivity of 88% and specificity of 76% in the diagnosis of bronchopneumonia in a child having respiratory distress and wheeze. Leukocyte count was elevated in 17500 in 36 children in 50 cases of bronchopneumonia with sensitivity of 72% and specificity of 100%.

Hence it is concluded by the study that any child <1 year presenting with respiratory rate ≥54 / minute and having temperature of 37.6ºc and above more likely suffer from pneumonia especially if rate is counted after nebulisation. Similarly any infant presenting with running nose, audible wheeze, respiratory rate <54, temperature <37.6°C is likely to present with viral or allergic airway disease. Especially the rate is recorded after nebulisation and x-ray if the situation warrants.

Likewise in children in the age group 12-60 months , respiratory rate ≥44 and temperature ≥37.6°C are more likely to have pneumonia especially if the rate is counted after nebulisation.

Additionally, if lab support is available, leukocytosis >16250 and >13650 with above clinical signs in a child can reasonably predict that the child is suffering from

bacterial pneumonia in 6-11 months and 12 to 60 months respectively.

The study recommends that nebulisation services be made available in primary health centers and redefined tachypnea as an indicator of pneumonia if respiratory rate is >54 in infants and >44 in children between 12-60 months even after nebulisation.

Limitation of the study

This study needs to be validated in community settings by the primary health care provider.

Different geographical represents and presence or absence of pollution may alter the predictive ability of the tachypnea.

CONCLUSION

It can be concluded from the study that hyper-reactive airway disease can be differentiated from pneumonia, to a reasonable extent on the basis of clinical features like fever, RR, and simple investigation like leukocyte count. This may help in rational management with antibiotics, bronchodilators and steroids in these children. This study offers possibility of redefining the current algorithm by incorporating simple predictors that have potential application to the para-medical personnel. Our study indicates the need for initiating multi-centric trials in diverse settings to confirm or refute the findings.

A confirmation has practical implication for refining the current case management of a child presenting with difficult breathing. In this context, the feasibility of simplified delivery of aerosolized bronchodilator therapy through a metered dose inhaler and nebulizer merits exploration. Prevention of over-use of antibiotics and the obvious economic advantage are the major advantages of the refined / re-defined algorithm used.

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PROFORMA

Name :

IP No. :

Age :

Sex :

Date of Admission:

Clinical Findings	Day 1	Day 2	Day 3	Day 4	Day 5
Fever					
RR					
Cough					
Nose Block or Discharge					
SCR/ICR					
Wheeze					
Crepts					
Others					

Investigations:

TC :

DC :

PS :

XRAY Chest Report :

Diagnosis :

Treatment :

Date of Discharge :